## NEW HOT PAPERS - 2009

**July 2009**

PDF

**Nader G. Abraham & Attallah Kappas talk with *ScienceWatch.com* about this month's New Hot Paper in the field of Pharmacology & Toxicology.**

**Article Title: Pharmacological and clinical aspects of heme oxygenase**

Authors: Abraham, NG;Kappas, A

Journal: PHARMACOL REV, Volume: 60, Issue: 1, Page: 79-127, Year: MAR 2008

* New York Med Coll, Dept Med & Pharmacol, Basic Sci Bldg, Valhalla, NY 10595 USA.
* New York Med Coll, Dept Med & Pharmacol, Valhalla, NY 10595 USA.
* Rockefeller Univ Hosp, New York, NY 10021 USA.

---

The paper collates and brings up-to-date much of the current knowledge relevant to pharmacology and to clinical medicine concerning the enzyme heme oxygenase (HO), which catabolizes the breakdown of the oxygen-carrying respiratory pigment called heme. In this process, heme is converted to the bile pigment bilirubin; carbon monoxide is generated, and the iron atom, which is complexed by the porphyrin ring of the molecule, is released.

The background to the discovery of HO is important to appreciate. The Laboratory of Pharmacology, at The Rockefeller University Hospital, in which this work was done, was established in 1967 by Professor Attallah Kappas, who then headed the laboratory and also served subsequently as Physician-in-Chief of The Rockefeller Hospital and Vice-President of the University.

The research program of the Kappas group generally focused on problems of heme biochemistry and pharmacology. The group conducted a broad and sustained program of research on the hereditary and acquired disorders of porphyrin-heme synthesis known as the porphyrias—a family of disorders resulting from deficiencies in the various enzymes of heme biosynthesis; on the role of specific components of the human diet in regulating the metabolism of drugs, hormones, and other chemicals by the heme-containing proteins in the liver known as the cytochromes P450; and also on genetic and acquired disorders associated with severe hyperbilirubinemia (jaundice)—especially severe jaundice in newborns.

The problem of how the heme molecule was catabolized into what we can call its component parts was a subject of great interest to many biochemists over many years. The problem was apparently solved in the late 1960s by other investigators whose research led them to the conclusion that the terminal step in the oxidative degradation of heme—i.e., the cleavage of the tetrapyrrole ring of heme to form the linear tetrapyrrole biliverdin, the immediate precursor of bilirubin—was carried out by a species of cytochrome P-450.

The similarity between the elements of the heme catabolic sequence and other oxidative systems which had been clearly shown to be dependent on cytochrome P-450 seemed compelling. It was concluded therefore that the heme ring was oxidatively ruptured by a form of cytochrome P-450—and the issue of how heme was degraded to bile pigment seemed resolved.


*Coauthor*
*Attallah Kappas*

Nevertheless, there were several features of heme degradation and the cytochrome P-450-dependent oxidative reactions involving drugs and other substances which did not entirely match, and this was intriguing as a biochemical problem. Professor Kappas decided to study this problem further in order to clarify these dissimilarities and also because of the important clinical research implications—if it could be shown that HO could be regulated by some means other than by the action of its natural substrate heme, a well-known inducer of HO.

The project was undertaken by two members of the laboratory group who, remarkably, had not previously worked in the porphyrin-heme field and thus they were presented with an opportunity to enter this new and interesting field. The end result was that it proved possible to entirely separate the liver enzyme known as HO from any of the heme-containing cytochromes P-450—heme is a substrate for HO but not an integral component of the enzyme, as is the case for cytochrome P-450—and therefore, to begin its purification, work which finally clarified the mechanism of heme breakdown.

In addition, the inducibility of the enzyme by non-heme containing compounds, such as inorganic and organometals was established, thus permitting studies on the metabolic consequences of the upregulation of HO activity by chemicals of varied structure. This aspect of HO is now recognized to have potentially important pharmaceutical significance.

The development of synthetic heme analogues which could competitively inhibit HO activity followed and thus, the possibility was further offered of down-regulating, as well as up-regulating the enzyme activity, in circumstances where one or another action might prove useful.

The examination of the role of the HO system, including the heme catabolism products CO, biliverdin/bilirubin, and the iron released in the process of heme degradation, has grown substantially in importance to the discipline of pharmacology and also in its implications for clinical medicine during the past three decades.

The HO system has been found to be crucial in cellular defense for numerous diseases, among which are diabetes, hypertension, heart diseases, inflammation, transplantation, neurodegenerative and ageing processes, and the metabolic syndrome. As a result, research has been expanded from a reexamination of the heme degradation process to the role of the catabolic products of heme, as well as the metabolic processes which are affected by perturbations of heme metabolism.

The fact that our paper has been so highly cited indicates the important role which HO is now recognized to play in diverse metabolic, physiological, and pathological circumstances. It is already apparent that the up-or downregulation of HO activity by chemical or genetic means may have beneficial clinical consequences (e.g., see N.G. Abraham and A. Kappas: "Heme Oxygenase and the Cardiovascular-Renal System," *Free Radical Biology and Medicine* 39: 1-25, 2005) and the increase in the number of citations in PubMed (17,000 articles in 2007-2008 alone attests to the importance of the HO system within the research community.

The successful application of HO inhibitors to interdict the development of severe jaundice in newborns was accomplished by our group—this was the first application of the principle of regulating HO for clinical purposes—and provides a clear demonstration that this enzyme represents a fruitful target for drug development. The successful development of therapies based on the ability to regulate HO could have profound implications since the targeted diseases exert a huge cost, both to the patients, in terms of morbidity and mortality, and to the healthcare system which is responsible for their care.

**Nader G. Abraham, Ph.D.**
**Professor of Pharmacology**
**New York Medical College**
**Valhalla, NY, USA**
**Adjunct Professor**
**The Rockefeller University**

New York, NY, USA
Web

Attallah Kappas, M.D.
Sherman Fairchild Professor
Head, Laboratory of Pharmacology
and Physician-in-Chief, emeritus
The Rockefeller University
New York, NY, USA
Web

KEYWORDS: SPONTANEOUSLY HYPERTENSIVE-RATS; HUMAN-ENDOTHELIAL-CELLS; NECROSIS-FACTOR-ALPHA; SMOOTH-MUSCLE-CELLS; NF-KAPPA-B; GENE PROMOTER POLYMORPHISM; NITRIC-OXIDE SYNTHASE; BONE-MARROW CULTURE; HEAT-SHOCK-PROTEIN; K-CA CHANNELS.

PDF

back to top

2009 : July 2009 - New Hot Papers : Nader G. Abraham & Attallah Kappas

Science Home | About Thomson Reuters | Site Search